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Serap Erdal and Susan N. Buchanan

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Serap Erdal¹ and Susan N. Buchanan²

¹Division of Environmental and Occupational Health Sciences, School of Public Health, University of Illinois at Chicago, Chicago, Illinois.

²Department of Occupational Medicine and Department of Family Medicine, College of Medicine, University of Illinois at Chicago, Chicago, Illinois.

The page proofs should be sent to:

Dr. Serap Erdal
Environmental and Occupational Health Sciences
School of Public Health
2121 West Taylor Street
Chicago, IL 60613

Tel. No: (312) 996-5875
Fax No: (312) 413-9898
e-mail: erdal@uic.edu

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Abbreviations:

ADA: American Dental Association
EDI: Estimated Daily Intake
AT: Averaging Time
CDC: Centers for Disease Control
CTE: Central Tendency Estimate
ED: Exposure Duration
EF: Exposure Frequency
HI: Hazard Index
HQ: Hazard Quotient
IRIS: Integrated Risk Information System
LOAEL: Lowest Observed Adverse Effect Level
NAS: National Academy of Sciences
RfD: Reference Dose
RME: Reasonable Maximum Estimate
TUIL: Tolerable Upper Intake Level
WHO: World Health Organization
USDA: United States Department of Agriculture
USEPA: United States Environmental Protection Agency

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Abstract

The prevalence of dental fluorosis in the United States has increased during the last thirty years. In this study, a mathematical model commonly employed by the USEPA is used to estimate average daily intake of fluoride via all applicable exposure pathways contributing to fluorosis risk for infants and children living in hypothetical fluoridated and non-fluoridated communities. Hazard Quotient for each exposure pathway and Hazard Indices are also estimated for exposure conditions representative of central tendency (CTE) and reasonable maximum exposure conditions (RME). The exposure pathways considered are uptake of fluoride via fluoridated drinking water, beverages, cow's milk, foods, and fluoride supplements for both age groups. Additionally, consumption of infant formula for infants and inadvertent swallowing of toothpaste while brushing and soil for children are also considered. The cumulative daily fluoride intake in fluoridated areas was estimated as 0.20 and 0.11 mg/kg-d for RME and CTE scenarios, respectively, for infants. On the other hand, the RME and CTE estimates for children were 0.23 and 0.06 mg/kg-d, respectively. In areas where municipal water is not fluoridated, our RME and CTE estimates for cumulative daily average intake were 0.11 and 0.08 mg/kg-d for infants and 0.21 and 0.06 mg/kg-d for children, respectively. Our theoretical estimates are in good agreement with measurement-based estimates reported in the literature. Although CTE estimates were within the optimum range for caries prevention the RME estimates were above the upper tolerable intake limit. This suggests that a segment of the children population may likely be at risk for fluorosis.

Introduction

Nearly two-thirds of the United States population receives drinking water from municipalities that add fluoride to their water systems to prevent dental caries (CDC 2002). The Centers for Disease Control and Prevention (CDC) hails fluoridation of drinking water as one of the ten great public health achievements of the 20th century (CDC 1999). The first Surgeon General's Report on Oral Health in America credits fluoridation for dramatically lowering caries rates. Several studies have shown caries reduction of up to 60% following fluoridation (US DHHS 2000).

While the efficacy of drinking water fluoridation is well-accepted by the scientific community and policy makers, the benefits are not without consequence. Ingestion of fluoride during a child's formative years of enamel development can cause dental fluorosis – a condition marked by permanent, often pronounced staining of adult teeth. Reports of fluorosis prevalence in North American children range widely depending on public water fluoridation status (Clark 1994; Mascarenhas 2000; Riordan and Banks 1991; Tabari et al 2000). In the National Survey of Dental Caries in US school children (1986-87) 22% of children examined had fluorosis (Brunelle 1989). In 1998, 69% of children ages 7-11 years examined in a suburban Boston pediatric practice were found to have fluorosis (Morgan et al. 1998). Children from a fluoridated community in North Carolina showed a prevalence of 78% (Lalumandier and Rozier 1995). In non-fluoridated communities, fluorosis prevalence reported in a number of studies conducted from 1990 -2000 ranges from 3 to 45% (Clark 1994; Mascarenhas 2000; Riordan and Banks 1991; Tabari et al. 2000).

In addition to fluoridated drinking water, several studies point to other sources of fluoride (e.g., fluoride toothpaste, fluoride supplements, infant formula and beverages produced with fluoridated water, food grown in soil containing fluoride or irrigated with fluoridated water, and cow's milk from livestock raised on fluoride-containing water and feed, and soil) contributing to overall fluoride intake and therefore may contribute to dental fluorosis (Fomon et al. 2000; Jackson et al. 2002; Levy 1994, Levy et al. 2001, Pendrys and Stamm 1990). In this study we evaluate total fluoride intake and fluorosis risk of infants and children using quantitative health risk assessment. While several published studies in the past decade have measured daily intake rates of fluoride from various sources such as diet, toothpaste, and infant formula (Fomon et al. 2000; Jackson et al. 2002; Levy 1994, Levy et al. 2001, Pendrys and Stamm 1990), none has systematically considered cumulative fluoride intake from all significant sources combined. We performed a comparative analysis of fluoride intake in fluoridated and non-fluoridated communities by characterizing the exposures via all significant exposure pathways applicable for infants and children in two age groups: infants less than 1 and children 3-5 years old. The analysis was limited to formula-fed infants only.

Study Methodology

We utilized the risk assessment paradigm developed by the National Academy of Sciences (NAS 1983), which is commonly used by federal environmental agencies in the U.S. to inform decisions regarding risk priorities, risk ranking, and health-based environmental standard development (USEPA 1989; 1995). This risk assessment model, in general, consists of the following four steps: hazard identification, dose-response assessment, exposure assessment and

risk characterization. We applied this four-step risk assessment paradigm to quantitatively estimate exposure pathway-specific and cumulative daily average intake of fluoride by infants and children. We should note that the significance of dental fluorosis has been controversial at times and there is a differing perspective by differing agencies and organizations charged with protecting the public health. While the EPA considers fluorosis as a cosmetic effect rather than an adverse health effect the World Health Organization (WHO) treats fluorosis as an adverse health effect affecting millions of people around the world (WHO 2001; 2002). In this paper, cumulative daily dose and health risk are estimated to determine the exposure pathways and conditions resulting in increased likelihood for dental fluorosis in children, with the vision that such information would be beneficial in identifying exposure pathways of concern and in managing risks for fluorosis. Therefore, application of a quantitative risk assessment model is appropriate for determining acceptability of risks associated with exposure to any chemical, independent of whether that chemical has a specific adverse health effect.

Hazard Identification: There are a number of health effects associated with fluoride ingestion, ranging from nausea to neurotoxic effects to death (Mullins et al. 1998; Vogt et al. 1982). The effect of concern in our risk assessment is the most common effect of chronic ingestion of fluoride in the form of fluoride salts— dental fluorosis. Fluorosis occurs as permanent teeth are forming and is characterized by a permanent hypomineralization. It appears initially as white streaks or mottling on the tooth enamel. With continued systemic exposure to fluoride, these streaks become white patches progressing to brown stains and pitting. The exact age at which teeth are most vulnerable is somewhat controversial with opinions ranging from the prenatal stage of permanent tooth formation to ages 3-6, when maximal mineralization occurs. It is

generally accepted, however, that after ages 6-8, teeth are no longer susceptible to the adverse effects of fluoride.

Dose-Response Assessment: The U.S. Environmental Protection Agency (EPA) publishes a database of toxicity values derived from dose-response relationships relating exposure (dose) to health effect for various chemicals found in the environment. This database, called the Integrated Risk Information System (IRIS), provides the toxicity values (e.g., Reference Dose, RfDs) for individual noncarcinogenic chemicals. The RfD is an estimate of the daily exposure to children and adults that is likely to be without appreciable risk of deleterious effects during a lifetime with uncertainty spanning perhaps an order of magnitude. The RfD published by the EPA for fluoride is 0.06 mg/kg-d and is based on the NOAEL of 0.06 mg/kg-d and uncertainty and modifying factors of unity (USEPA 2003). Uncertainty factors were not deemed necessary since NOAEL was derived from a chronic study focusing on the critical effect (i.e., dental fluorosis) in a sensitive population of humans (i.e., children). The scientific basis and rationale of the fluoride RfD (Burt 1992; Hodge 1950) can be found in IRIS, and is beyond the scope of this paper.

Exposure Assessment: The populations of interest, the pathways by which exposure may occur, and the magnitude, frequency, and duration of these potential exposures are identified in this step. The population of interest in this analysis is infants (< 1 year old) and children (3-5 years old). An estimated daily intake (EDI) is calculated for each exposure pathway using a number of exposure parameters using Equation 1 (USEPA 1992):

$$EDI = \frac{C \times IR \times EF \times ED \times AF \times CF}{BW \times AT}$$

Equation 1

ETI	=	Estimated daily intake (mg/kg-d)
C	=	Concentration in a specific medium (mg/L or mg/kg)
IR	=	Ingestion or Intake Rate (mg/d)
EF	=	Exposure frequency (d/yr)
ED	=	Exposure duration (yr)
AF	=	Absorption Factor (unitless)
CF	=	Conversion Factor (10^{-6} kg/mg)
BW	=	Body weight (kg)
AT	=	Averaging time (d)

The exposure pathways considered are:

Pathway A—Ingestion of fluoridated public drinking water

Pathway B—Ingestion of soft drinks and fruit juices (beverages)

Pathway C— Consumption of infant formula

Pathway D—Ingestion of cow's milk

Pathway E— Consumption of foods

Pathway F— Incidental ingestion of soil

Pathway G—Ingestion of fluoride supplement tablets

Pathway H—Incidental ingestion of fluoride toothpaste

The exposure pathways A, B, C, D, E, and G are included in the estimation of cumulative fluoride intake for infants. All exposure pathways except Pathway C (infant formula) are included to estimate cumulative fluoride intake of children. Using Equation 1, the EDI for each exposure pathway is calculated by identifying appropriate values for exposure parameters (e.g., concentration, ingestion rate, body weight, exposure frequency, exposure duration) for the two age groups. Two values for each exposure parameter are calculated in characterizing potential exposures: one value to represent an average or “central tendency exposure” (CTE) and another value for the high-end or “reasonable maximum exposure” (RME), which is intended to represent a plausible worst exposure (USEPA 1989). The RME estimates are often used by the EPA when making regulatory decisions and recommendations regarding acceptability of health risk to humans.

Age-specific values used in the calculation for EDI (Equation 1) can be found in Table 1. The *EPA’s Child-Specific Exposure Factors Handbook* was consulted for the estimation of average daily fluoride intake via all the exposure pathways except consumption of infant formula (Pathway C), ingestion of fluoride supplements (Pathway G) and incidental ingestion of toothpaste (Pathway H) (USEPA 2002). A more in depth discussion about the rationale for exposure pathway-specific exposure parameters shown in Table 1, specifically fluoride concentrations in each exposure medium, are presented below. Exposure frequency was assumed to be 365 days per year. Exposure duration was one year for infants and two years for children. Exceptions to these for EF and ED are also noted below. The averaging time (AT) is equal to exposure duration (ED) times 365 days/year. Average body weight of 8.4 kg for 2-12 month old male and female infants, respectively, in the US population based on survey data from

1988 to 1994 was used as the body weight of infants. For 3-5 year old group, the mean body weight was estimated in a similar fashion as 17.2 kg using the same data source (USEPA 2002). The estimation of EDI also requires information on absorption (or bioavailability) factor. Fluoride is readily absorbed from the GI tract with estimates of absorption ranging from 75-100% (ATSDR 2001; Ekstrand and Ehrnebo 1980). In toothpaste, sodium fluoride is 100% available as fluoride ion (Alhaique et al. 1982), and studies show a linear relationship between amount of toothpaste ingested and serum levels of fluoride (Ekstrand and Ehrnebo 1980). Therefore, the absorption factor (AF) in Equation 1 is assumed to be unity.

Pathway A – Ingestion of Drinking Water: The US Public Health Service sets optimal drinking water levels based on geographic temperature bands and corresponding water consumption rates (Lalumandier and Jones 1999). The recommended level of fluoride concentration in temperate zones is 1 ppm, or 1 mg/L. A recent study conducted by the U.S. Department of Agriculture (USDA) which measured fluoride content of nationally representative municipal water samples from 24 Consolidated Metropolitan Statistical Areas in the U.S. revealed that either water is fluoridated and contains approximately 1 mg/L of fluoride or it is not fluoridated with undetectable fluoride concentration (Miller-Ihli et al. 2003). The USDA study found that about 40% of the water samples were fluoridated with a mean concentration of 1.01 ± 0.15 mg/L. We assumed that the water in non-fluoridated areas does not contain any fluoride.

The use of bottled water as the primary source of drinking water has increased in the U.S. The American Dental Association (ADA) recently called for labeling of fluoride concentrations on bottled water due to increased use of bottled water not only as a drinking water source, but also in preparation of infant formulas, and various foods. Bartels et al. (2000) examined fluoride

concentrations of five commercially available bottled water products. The results indicated that although there were significant differences in fluoride concentrations among different brands and between different batches from the same brand, all products had fluoride concentrations lower than the ADA-accepted standard for optimally fluoridated water (i.e., 0.7 to 1.2 mg/L dependent on the average maximum daily air temperature of an area). Due to widespread use of bottled water being a recent phenomenon, there are limited data to ascertain how bottled water intake is affecting children's teeth. Our intake/risk estimates for infants and children consuming non-fluoridated tap water would most likely be equivalent to intake/risk estimates of those consuming bottled water as their drinking water source due to the fact that the majority of the bottled water in the U.S. is currently not fluoridated. However, this may change in the future due to pressure from consumer groups and federal/state regulatory agencies.

Pathway B – Ingestion of Soft Drinks and Fruit Juices: The ingestion of soft drinks and commercially prepared fruit juices has more than doubled in the last 25 years (Levy 1994). Because these beverages are usually prepared with fluoridated water they can be a significant source of fluoride. Pang et al. (1992) reported the fluoride content of sodas, juices, punches, tea, and Gatorade purchased in North Carolina. Fluoride levels were highly variable, ranging from <0.1 to 6.7 mg/L. We used the weighted average of these reported concentrations (0.76 mg/L) in calculating the EDI for this pathway.

Pathway C – Consumption of Infant Formula: Infant formula processed with fluoridated water may be a significant source of fluoride in infants. In 1979, due to the concern about fluoride intake in infants, formula manufacturers voluntarily agreed to lower the concentration of fluoride in their products (Fomon et al. 2000; Levy 1994). However, fluoridated water used to

reconstitute or dilute powdered or concentrated preparations remains a concern. An average concentration of 0.65 mg/kg fluoride is used in the EDI calculation. This concentration was derived based on a survey of fluoride concentrations in ready-to-use formula (mean: 0.23 mg/kg fluoride), concentrated liquid (mean: 0.6 mg/kg fluoride), and powdered concentrate (1.13 mg/kg fluoride) sold in retail stores in the U.S. (ATSDR 2001; Dabeka and McKenzie 1987).

The intake rate of infant formula was estimated from feedings recommendations in *Nelson Textbook of Pediatrics* (Behrman and Vaughn 2000).

Pathway D – Ingestion of Cow’s Milk: Cows ingesting fluoridated water or feed processed with fluoridated water produce milk containing fluoride. The mean fluoride concentration of 0.041 mg/kg (range: 0.007-0.086 mg/kg) reported in a Canadian study (Dabeka and McKenzie 1987) which surveyed fluoride concentrations in 68 samples of milk sold in retail stores across Canadian provinces was used in this analysis.

Human breast milk contains very low levels of fluoride (0.004 mg/L in non-fluoridated and 0.01 mg/L in fluoridated areas) even when intake by the mother is high (Fomon et al. 2000; Levy 1994). Moreover, the percentage of exclusively breastfed infants at 6 months of age in the U.S. was only 22% in 1995 (Ryan 1997). For these reasons, only formula-fed infants are included in this analysis. It should be emphasized that exclusively breast-fed infants will have a much lower average daily fluoride intake for the duration of the breastfeeding period than formula-fed infants.

Pathway E – Consumption of Food: Dabeka and McKenzie (1995) determined fluoride concentrations in individual food items and food composites in various categories (milk and dairy products, meat and poultry, soups, bakery goods and cereals, vegetables, fruits and fruit juices, fats and oils, sugar and candies, beverages, and other miscellaneous items) purchased in Winnipeg, Canada. Food categories with the highest mean fluoride levels were fish (2.118 mg/kg), soups (0.606 mg/kg), and beverages (1.148 mg/kg). The mean fluoride concentration in all samples including milk, various beverage and fruit juice, and tap water samples was 0.325 mg/kg, ranging from 0.011 to 4.970 mg/kg. Using these data, we estimated the mean fluoride concentration of 0.262 and 0.29 mg/kg fluoride in foods potentially consumed by infants and children, respectively. This estimate does not include milk, beverages and fruit juices, and tap water since these are treated separately in our analysis. For infants, certain food items were excluded from diet (e.g., cold cuts, lunch meat, cured meats, honey) and fluoride exposure due to food consumption was limited to eight months starting at four months of age.

Pathway F – Incidental Ingestion of Soil: Children inadvertently ingest soil due to normal hand-to-mouth behavior. Industrial sites, hazardous waste sites containing fluoride, and soil contaminated with phosphate-containing fertilizers may have higher levels of fluoride. We used the mean fluoride concentration in soils and other surface materials in the U.S. (430 mg/kg; range: 10-37,000 mg/kg) (ATSDR 2001) in the calculation of the EDI for the incidental soil ingestion pathway. Since children less than 1 year old are not ambulatory, the average daily fluoride intake for this pathway is calculated for children 3-5 years old only.

Pathway G – Ingestion of Fluoride Supplements: Ingestion of fluoride supplements can be a major exposure pathway for some children. These supplements are prescribed to infants and

children in areas that lack fluoridated public water supplies. Although several studies indicate that supplements are often prescribed inappropriately to children in fluoridated areas, (Lalumandier and Rozier 1995; Pendrys and Katz 1989), we assumed only children living in non-fluoridated areas receive supplementation. The ADA, the American Academy of Pediatric Dentistry, and the American Academy of Pediatrics recommend supplemental fluoride intake of 0.25 and 0.5 mg/d for the age group of 6 months-3 years old and of 3-6 years old, respectively, in non-fluoridated water areas (CDC 2001). Following the recommended dosing schedule for infants, exposure was limited to six months for infants less than 1, starting at six months of age.

Pathway H – Incidental Ingestion of Toothpaste: Because over 90% of toothpaste sold in North America is fluoridated, many children are exposed to fluoride through incidental ingestion of toothpaste. Toothpastes specifically flavored for children have been linked with use of larger quantities of toothpaste, increasing the importance of this pathway (Levy 1994). The recommended concentration for fluoride ion in the U.S. is generally 1,000 mg/kg (ATSDR 2001; CDC 2001). The CTE and RME ingestion rates of toothpaste used in the estimation of EDI were the average (0.26 g toothpaste per brushing) and 90th percentile (0.77 g toothpaste per brushing) compiled from eleven studies (CDC 2001; Levy 1993; Levy 1994). We assumed a brushing frequency of once daily for the CTE and three times daily for the RME. This pathway was excluded from the estimation of cumulative fluoride intake for infants (< 1 years old) since several studies show that many in this age group do not have their teeth brushed (Levy et al. 1997; Tabari et al. 2000).

The EDI representing CTE and RME scenarios are calculated for each exposure pathway discussed above using Equation 1. Cumulative daily fluoride intake is estimated by adding EDI

values for infants and children living in fluoridated and non-fluoridated areas using Equations 2-5. In non-fluoridated areas, fluoride concentration in drinking water was assumed to be zero, thus intake through ingestion of drinking water was not considered. On the other hand, it was assumed that no intake via ingestion of fluoride supplements would occur in fluoridated areas.

For infants living in fluoridated areas:

$$Cum. ADI_{<1,f} = ADI_A + ADI_B + ADI_C + ADI_D + ADI_E \quad \text{Equation 2}$$

For children 3-5 years old living in fluoridated areas:

$$Cum. ADI_{3-5,f} = ADI_A + ADI_B + ADI_D + ADI_E + ADI_F + ADI_H \quad \text{Equation 3}$$

For infants living in non-fluoridated areas:

$$Cum. ADI_{<1,nf} = ADI_B + ADI_C + ADI_D + ADI_E + ADI_G \quad \text{Equation 4}$$

For children 3-5 years old living in non-fluoridated areas:

$$Cum. ADI_{3-5,nf} = ADI_B + ADI_D + ADI_E + ADI_F + ADI_G + ADI_H \quad \text{Equation 5}$$

Risk Characterization: The Hazard Quotient (HQ), as an estimate of the RME and CTE health risks associated with fluoride exposure via each exposure pathway, is estimated by integrating

exposure and toxicity information. The sum of the HQs, the Hazard Index (HI), is then calculated using Equation 6, which represents the total fluoride intake risk.

$$HI_{3-5} = \frac{Cum. ADI_{3-5}}{RfD} = \sum_{pathway=1}^n HQ_{3-5}; \quad HI_{<1} = \frac{Cum. ADI_{<1}}{RfD} = \sum_{pathway=1}^n HQ_{<1} \quad \text{Equation 6}$$

Results

Numerical results of the CTE and RME EDI estimates for each pathway and for each age group are shown in Table 2. Figure 1 depicts the RME EDI estimates for infants and children. For infants, while drinking water (52%) and infant formula (39%) are the two most significant sources contributing to cumulative daily fluoride intake in fluoridated areas, infant formula (71%), fluoride supplement (13.4%) and food (12.9%) are the sources of importance in non-fluoridated areas. For children, toothpaste (57%), drinking water (22%), and food (9%) in fluoridated areas and toothpaste (63%), fluoride supplement (14%) and food (10%) in non-fluoridated areas contribute significantly to the cumulative daily intake under the RME conditions.

Table 3 and 4 show the HQ and HI values estimated for infants and children for each exposure scenario. Table 4 also documents the estimates of cumulative EDI applicable to each exposure group living in fluoridated or non-fluoridated communities. All of the HI values are around unity for all CTE estimates, slightly elevated for infants living in fluoridated areas. On the other hand, all HI estimates for the RME scenario are greater than unity, indicating that cumulative daily fluoride intake is greater than the safe dose level established by the EPA for fluoride. Therefore,

there may be a segment of both populations, who may be at risk of developing fluorosis due to exposure to fluoride via exposure pathways studied in this analysis, under the specified RME conditions. Figure 2 illustrates the HI estimates for each exposure group in relation to the acceptable standard of unity for HI. It is interesting to note that all exposure pathway-specific HQ values are less than or around unity for infants and children under the CME conditions as shown in Table 3. However, fluoridated drinking water ingestion and consumption of infant formula for infants and incidental ingestion of toothpaste by children only are associated with HQ values slightly greater than unity under the RME conditions, which result in HI estimates greater than unity.

The cumulative daily fluoride intake in fluoridated areas was estimated as 0.20 and 0.11 mg/kg-d for RME and CTE scenarios, respectively, for infants. On the other hand, the RME and CTE estimates for children were 0.23 and 0.06 mg/kg-d, respectively (Table 4). In areas where municipal water is not fluoridated, our RME and CTE estimates for cumulative daily average intake were 0.11 and 0.08 mg/kg-d for infants and 0.21 and 0.06 mg/kg-d for children, respectively. For infants, cumulative fluoride intake is all due to dietary sources in fluoridated areas. In non-fluoridated areas, dietary intake constitutes about 87% (0.1 mg/kg-d) and 90% (0.07 mg/kg-d) of the cumulative intake for infants and about 18% (0.04 mg/kg-d) and 43% (0.02 mg/kg-d) of the cumulative daily intake for children under RME and CTE scenarios, respectively. In fluoridated areas, dietary intake was found to constitute 38% (0.09 mg/kg-d) and 73% (0.05 mg/kg-d) of the cumulative intake for children for RME and CTE scenarios, respectively. These results demonstrate that total fluoride exposure is mainly due to dietary sources for infants, however non-dietary sources (e.g., fluoride supplements, toothpaste) gain

importance for children's exposure to fluoride. The average optimum dietary fluoride intake by children living in fluoridated communities is found to be close to 0.05 mg/kg-d (range: 0.02-0.1 mg/kg-d) (IOM 1999). The Institute of Medicine (IOM) recently established a Tolerable Upper Intake Level (TUIL) of 0.1 mg/kg-d for infants, toddlers, and children through the age of 8 years of age, based on the Lowest Observed Adverse Effect Level (LOAEL) for moderate fluorosis, using dietary fluoride intake data (IOM 1999). All of our dietary intake estimates fall within the range of 0.02-0.1 mg/kg-d, except for infants living in fluoridated areas under the RME scenario, primarily due to ingestion of water pathway. Levy et al. (2001) also found that for children under 12 months of age, drinking water was a primary source of fluoride intake.

Discussion

A number of studies published in the literature have estimated total daily fluoride intakes from dietary sources and toothpaste ingestion. Pendrys and Stamm (1990) estimated fluoride intake from diet (water and beverages), supplements and toothpaste to be 0.07 (range: 0.04-0.2) and 0.08 (range: 0.05-0.21) mg/kg-d for 2-yr old children from fluoridated and non-fluoridated communities, respectively. These EDI estimates are similar to our estimates for 3-5 year old group, with the mean of 0.06 mg/kg-d in both fluoridated and non-fluoridated water areas. It is interesting to note that the high-end estimates reach to about 0.2 mg/kg-d in both analyses. Levy et al. (2001) estimated daily fluoride intake from water (including beverages), toothpaste, and fluoride supplements from birth to 36 months as part of a longitudinal study in Iowa. The estimated mean intakes were 0.06 mg/kg for 3 to 12 months age group, and 0.043 mg/kg-d for 20-36 months of age group. The 90th percentile values were 0.12 and 0.08 mg/kg-d for infants (3-

12 months old) and 3-year old children, respectively. On the other hand, the maximum fluoride intake estimates were significantly higher, amounting to 0.2 mg/kg-d for 3-year old children, and 0.9 mg/kg-d for infants. We estimated average intake levels of 0.05 and 0.06 mg/kg-d for <1 and 3-5 year-old age groups in our analysis for combined fluoride sources from water, beverage, fluoride supplement, and toothpaste, which are in agreement with the estimates of Levy et al. (2001). Our RME-EDI estimates for these four exposure pathways were 0.12 and 0.23 mg/kg-d for infants and children, respectively. Although the infant estimate is in agreement with the reported 90th percentile value, our RME for children is higher (close to maximum), potentially due to the fact that while we consider older children Levy et al. (2001) limits the maximum age studied to three. In addition, Levy et al. (2001) did not include intake of pre-packaged beverages like fruit juice and soda, and the amount of toothpaste used, and proportion ingested was estimated by parents, both of which may have led to underestimation of fluoride intake. Jackson et al. (2002) recently estimated average daily dietary intake of fluoride from food (including milk) and beverages using a food questionnaire and USDA intake rates for 3-5 year-old children living in fluoridated and non-fluoridated towns in Indiana. The children from the fluoridated town had an average fluoride daily intake of 0.033 mg/kg-d and a maximum intake of 0.062 mg/kg-d. On the other hand, children from non-fluoridated communities had an average of 0.028 mg/kg-d and a maximum intake of 0.058 mg/kg-d. Our EDI estimates for these pathways (milk, food, beverages) for the 3-5 year-old exposure group are slightly lower, with 0.04 and 0.02 mg/kg-d for RME and CTE scenarios, respectively. This may be due to the fact that our estimates for fluoride intake through milk, beverages, and food do not differentiate whether these sources come from fluoridated or non-fluoridated areas.

Prevention of dental caries, as established by numerous epidemiologic studies, has been such a dramatic public health achievement that the US Public Health Service has set a goal of an increase to 75% of the US population to be served by a fluoridated supply, in its Healthy People 2010 Initiative (US DHHS 2000b). However, the findings of this health risk assessment study support concerns that a segment of the infant and child population in the U.S. may be exposed to amounts of fluoride greater than the optimum level for caries prevention. We found that when only dietary exposure pathways are considered the EDI varies from 0.02 to 0.1 mg/kg-d in non-fluoridated communities, which is within the optimum range (IOM 1999). However, in fluoridated communities, this range was 0.05-0.2 mg/kg-d, with drinking water and infant formula being the primary contributors. When non-dietary sources were also considered, the cumulative EDI values significantly increased for children while there was a negligible difference between the dietary exposure and cumulative exposure for infants. For the 3-5 old age group, the use of fluoride supplements and, especially, inadvertent ingestion of toothpaste containing fluoride significantly increased the total fluoride intake by two to six fold under the RME scenario. However, drinking water, food, fluoride supplements, and toothpaste contributed in similar percentages (21-27%) to the cumulative EDI under the CTE scenario for children living in fluoridated communities.

Analysis of uncertainty is an essential component of risk assessment. In this study, a single point value for each of the exposure parameters was used. However, fluoride concentrations in drinking water, beverages fruit juices, and various food items are known to vary greatly (Jackson et al. 2002). Studies measuring fluoride concentration in beverages do not track products to their source to verify whether they were produced with fluoridated water (Heilman et al. 1999;

Jackson et al. 2002; Levy 1994; Pang et al. 1992). A child consuming only beverages prepared with non-fluoridated water would have a lower fluoride intake. Children brushing more or less often obviously increase or decrease their risk of swallowing toothpaste. Children using mouth rinses and gels and specially-flavored toothpaste may especially be increasing their fluoride intake. Due to the availability of scant data on intake rates of bottled water, this source was not considered. The increased reliance on bottled water as the primary drinking source among the U.S. population may change the dynamics of fluoride intake among the children, especially given the fact that many bottled water products do not contain any fluoride. That's why it is paramount to continuously track the prevalence of dental caries and fluorosis at specific life stages to determine trends and to apportion the total intake into each source. Tea leaves contain high levels of fluoride and brewed tea concentrations can range from 1 to 6 mg/L (IOM 1999; Pang et al. 1992). Children growing up in ethnic communities with frequent tea consumption may have increased high intake of fluoride (Cao et al. 1997; Jin et al. 2000). An epidemiologic investigation carried out in Mexico showed that boiling water doubled fluoride concentrations found in non-boiled water (Grimaldo et al. 1995). Thus, food or infant formula prepared with boiled water may result in increased fluoride intake through diet. The uncertainty associated with concentration of fluoride in drinking water, drinking water ingestion rate, consumption rates of beverages, cow's milk, and food, and fluoride supplement dosage can be classified as relatively high due to these estimates emanating from national-scale studies conducted by the EPA and USDA. The uncertainty for the rest of the exposure parameters fall into category of "low" or "medium to low." Fluoride concentrations in various exposure media (e.g., beverage, cow's milk, infant formula, food, soil) and incidental toothpaste ingestion rate are especially uncertain.

Therefore, the uncertainty in the overall intake and risk estimates can be described as “medium” at best, most likely as “medium to low.”

The hazard index which considers all exposure pathways applicable for a given exposure group was greater than unity in all cases under the RME conditions; and was within acceptable range in all cases except infants living in fluoridated areas under the CTE conditions. Therefore, it is likely that some infants and children receive fluoride levels in excess of those “likely to be without appreciable deleterious effects” (USEPA 2003) and are at risk for fluorosis. The findings of this study confirm the importance of considering all potentially applicable exposure pathways in estimating cumulative daily fluoride dose for scientifically sound decision-making in fluorosis risk management. Although the EDI associated with the ingestion of drinking water pathway (0.05 mg/kg-d—children/RME; 0.1 mg/kg-d—infants/RME; 0.02 mg/kg-d—children/CTE; 0.04 mg/kg-d—infants/CTE) does not exceed the optimum fluoride range in fluoridated areas by itself the cumulative intake exceeds the optimum range when other pathways are considered.

Therefore, one approach could be implementation of measures for reduction of fluoride intake from sources other than water in communities where tap water is fluoridated. The risk management for fluorosis in these communities could focus on preparation of infant formula for infants and ingestion of toothpaste for children. This finding emphasizes significance of educating parents and child-care specialists about fluorosis risk by public health practitioners, physicians, and dentists. The fluorosis risk can easily be reduced by supervision of children while brushing and preparation of infant formula with non-fluoridated water or purchase of infant formula constituted without the addition of fluoride. A significant role in fluorosis risk management is also assumed by the public health, medical and dental professionals by accurately

diagnosing fluoride needs of children by acquiring about all sources which are associated with fluoride exposure on a case-by-case basis and making informed and educated decisions about fluoride supplement prescription unique to each child.

On the other hand, a significant finding of our analysis is that, for both age groups living in non-fluoridated areas, while the cumulative intake is within the optimum range (0.06 mg/kg-d—children; and 0.08 mg/d—infants) under the CTE scenario the cumulative intake estimates are higher (0.21 mg/kg-d—children; and 0.11 mg/kg-d—infants), exceeding the optimum range, under the RME scenario. This raises questions about the continued need for fluoridation in the U.S. municipal water supply to protect against the risk of fluorosis. However, given the uncertainties inherent in this analysis, it is not possible to be conclusive. Further research with carefully-designed epidemiological studies with enough statistical power and strong exposure assessment component is essential and warranted to answer critical questions about the necessity of fluoridation in the presence of changes in dietary behavior of children and multiple sources of fluoride currently contributing to total intake. Cost-benefit analysis for fluoride should be a component of such studies. In addition, future studies should lead to collection of detailed exposure data for each exposure pathway so that more robust probabilistic risk assessment techniques, as opposed to point estimates of intake/risk presented here, could be applied to obtain distribution of fluoride intake/risk among children with quantitative measures of uncertainty.

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Table 1. Summary of exposure parameters used in the calculation of estimated daily fluoride intake.

Exposure Pathway	F Concentration	CTE Intake Rate ^a	RME Intake Rate
A. Drinking water ^b	1 mg/L	< 1 yo: 0.34 L/d 1-10 yo: 0.4 L/d (USEPA 2002 pg. 4-16)	< 1 yo: 0.88 L/d 1-10 yo: 0.9 L/d (USEPA 2002 pg. 4-16)
B. Beverages ^c	0.76 mg/L (Pang et al. 1992)	< 1 yo: 19 g/d 3- 5 yo: 269 g/d (USEPA 2002 pg. 3-38)	< 1 yo: 23.75 g/d 3-5 yo: 336.25 g/d (USEPA 2002 pg. 3-38)
C. Infant formula	0.65 mg/kg (ATSDR 2001)	198 ml/feeding, 4.4 feedings/day (Behrman and Vaughn 2000)	214 ml/feeding, 4.8 feedings/day (Behrman and Vaughn 2000)
D. Cow's milk ^c	0.041 mg/kg (Dabeka and McKenzie 1987)	<1 yo: 61 g/d 3-5 yo: 335 g/d (USEPA 2002 pg. 3-32)	<1 yo: 76.25 g/d 3-5 yo: 418.75 g/d (USEPA 2002 pg. 3-32)
E. Food ^b	<1 yo : 0.262 mg/kg 3-5 yo: 0.290 mg/kg (Dabeka and McKenzie 1995)	<1 yo: 223.6 g/d 3-5 yo: 691.9 g/d (USEPA 2002 pg. 3-59 and 3-32)	<1 yo: 612.7 g/d 3-5 yo: 1312.5 g/d (USEPA 2002 pg. 3-59 and 3-32)

F. Soil ^d	430 mg/kg (ATSDR 2001)	0.1 g/d (USEPA 2002 pg. 5-37)	0.4 g/d (USEPA 2002 pg 5-37)
G. Fluoride		6 mo-10: 0.25 mg/d NaF	6 mo-3yrs: 0.25 mg/d NaF
Supplements		3-6 yrs: 0.5 mg/d NaF (CDC 2001)	3-6 yrs: 0.5 mg/d NaF (CDC 2001)
H. Toothpaste	1000 mg/kg (ATSDR 2001)	3-5 yo: 0.26 g/brushing (Levy 1993) 1 brushing per day	3-5 yo: 0.77 g/brushing (Levy 1993) 3 brushings per day

^a Recommended mean intake rate as a combined estimate for males and females was used in all cases in the CTE scenario.

^b For drinking water and food consumption, 90th percentile of recommended intake rate was used in the RME scenario.

^c For consumption of beverages and cow's milk, a 25% more consumption than the mean was assumed in the estimation of RME daily intake.

^d For incidental ingestion of soil by children, upper percentile ingestion rate was used in the RME scenario.

Table 2. Estimated daily intake estimates for CTE and RME exposure scenarios.

Exposure Pathway	EDI – CTE (mg/kg-d)		EDI –RME (mg/kg-d)	
	< 1 yo	3-5 yo	< 1 yo	3-5 yo
A. Fluoridated Drinking water	0.04	0.023	0.10	0.052
B. Beverages	0.0017	0.012	0.021	0.015
C. Infant Formula	0.067	N/A	0.079	N/A
D. Cow's milk	0.0003	0.0008	0.00037	0.001
E. Food	0.0052	0.012	0.014	0.022
F. Soil	N/A	0.0025	N/A	0.01
G. Fluoride Supplements	0.0074	0.014	0.015	0.029
H. Toothpaste	N/A	0.015	N/A	0.13

N/A: These exposure pathways were assumed to be not applicable.

Table 3. The CTE and RME hazard quotient estimates for individual exposure pathways.

Exposure Pathway	HQ – CTE (mg/kg-d)		HQ –RME (mg/kg-d)	
	< 1 yo	3-5 yo	< 1 yo	3-5 yo
A. Fluoridated Drinking water	0.7	0.4	1.7	0.9
B. Beverages	0.03	0.2	0.04	0.2
C. Infant Formula	1.1	N/A	1.3	N/A
D. Cow's milk	0.005	0.01	0.006	0.02
E. Food	0.09	0.2	0.2	0.4
F. Soil	N/A	0.04	N/A	0.2
G. Fluoride Supplements	0.1	0.2	0.2	0.5
H. Toothpaste	N/A	0.2	N/A	2.2

N/A: These exposure pathways were assumed to be not applicable.

Table 4. Hazard indices and cumulative estimated daily intakes for exposure scenarios of concern.

Exposure Scenario	Hazard Index		Cumulative EDI (mg/kg-d)	
	CTE	RME	CTE	RME
Fluoridated area				
– < 1 yo old	1.9	3.3	0.11	0.20
Fluoridated area				
– 3-5 yo old	1.1	3.9	0.06	0.23
Non-Fluoridated area				
– < 1 yo old	1.4	1.8	0.08	0.11
Non-Fluoridated area				
– 3-5 yo old	0.9	3.5	0.06	0.21

Figure 1. RME daily intake estimates for each exposure pathway.

Figure 2. Hazard index estimates for each exposure scenario.

Figure 1

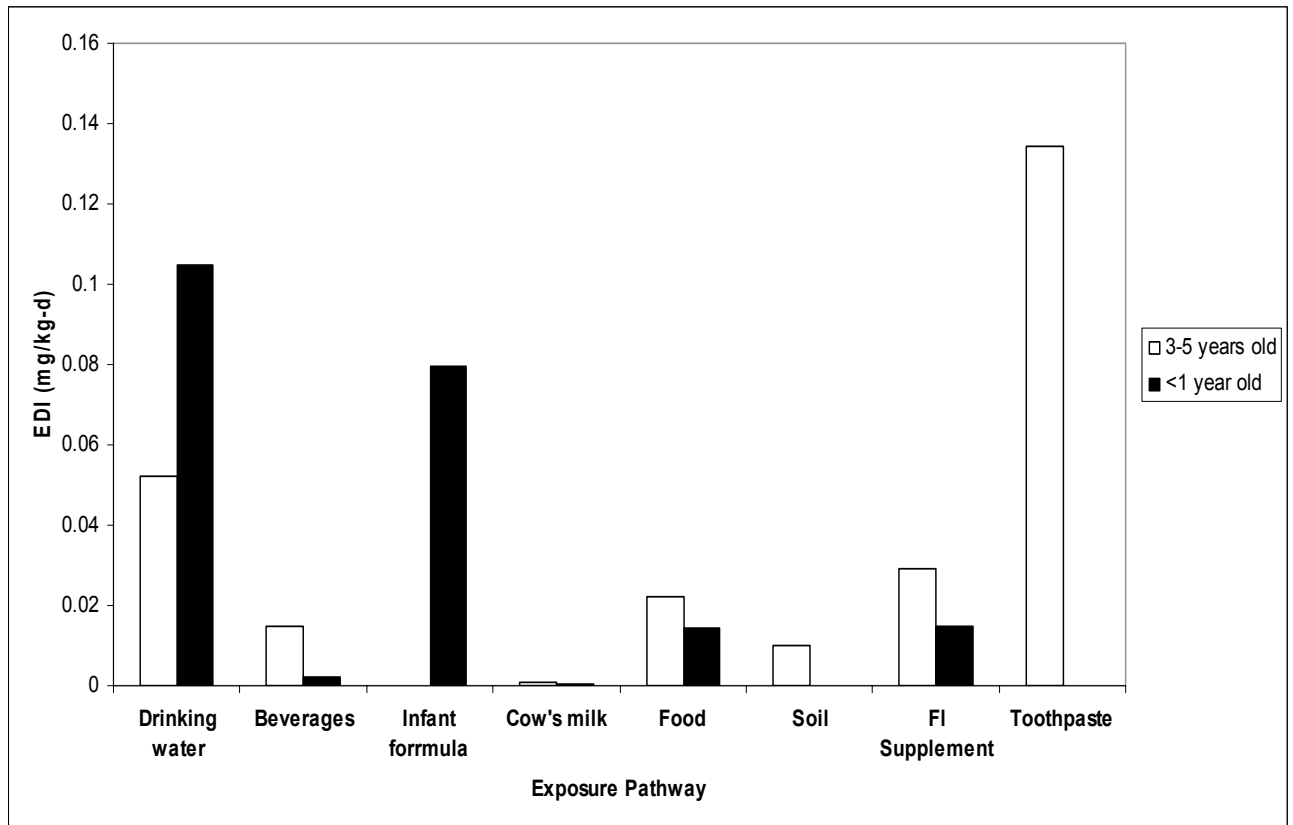


Figure 2

